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Effects of baroreceptor stimulation on performance of the Sternberg short-term memory task: A cardiac cycle time study

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Running head: Memory scanning and the cardiac cycle

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Highlights

- Activation of arterial baroreceptors can affect cortical activity
- Performance on the Sternberg memory task was examined as a function of the phase of the cardiac cycle
- Response latency per additional digit was greater for probe stimuli presented late compared to early in the cardiac cycle
- In line with the visceral afferent feedback hypothesis, natural baroreceptor stimulation interfered with memory retrieval and comparion processes

Abstract

Activation of arterial baroreceptors can affect cortical activity. Cardiac cycle time studies have established that natural variations in baroreceptor activation are associated with changes in basic sensorimotor function whereas few have investigated more complex cognitive function. Aiming to improve our understanding of this phenomenon, this study examined performance on the Sternberg memory task as a function of the phase of the cardiac cycle. In each trial, participants were shown either two or six digits followed by a probe digit that either had or had not been presented previously and were required to press one of two response buttons to indicate a match and mismatch, respectively. Response latency per additional digit was greater for stimuli presented late compared to early in the cardiac cycle whereas the zero intercept was greatest at the start of the cardiac cycle and reduced as the cycle progressed. These findings provide evidence that natural baroreceptor stimulation can affect complex cognitive processes, such as serial-comparison in short-term memory, as well as basic sensorimotor processes.

Keywords

Arterial baroreceptors; Cardiac cycle; Memory; Sternberg task.

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Introduction

The cardiac pulse pressure wave stretches the vessel walls to activate arterial baroreceptors in the aortic arch (Angell James, 1971) and carotid sinus (Mancia & Mark, 1983). Arterial baroreceptor afferents exhibit pulsatile activity, with maximum firing synchronous with increases in arterial pressure during the cardiac systole. At rest, blood is ejected from the left ventricle 70 ms after the peak of the R-wave of the ECG (Berntson, Lozano, Chen & Caccioppo, 2004). The resultant pressure pulse wave starts stretching the aortic and carotid baroreceptors 10-15 and 40-65 ms later, respectively (Rushmer, 1976). Aortic and carotid baroreceptor afferent signals travel up the aortic and carotid sinus nerve, terminate in the nucleus tractus solitarius within 10-15 ms, before projecting to brainstem areas, such as the nucleus ambiguous and medulla, within 100-150 ms. In turn, the nucleus tractus solitarius projects directly and indirectly (via the medulla and parabrachial nucleus) to the hypothalamus and indirectly to insular cortex via the parabrachial nucleus and thalamus (Willette, Punnen, Krieger, & Supru, 1984). It is apparent that heart beat contingent information is widely transmitted in the brain. For example, discharge rates of one in five cells in the amygdala and hippocampus are modulated by the phase of the cardiac cycle (Frysinger & Harper, 1989).

Behavioral researchers have capitalised on such naturally occurring variations in baroreceptor stimulation to investigate the effects of increases in blood pressure on task performance. In this form of the cardiac cycle time paradigm, responses to stimuli delivered while the baroreceptors are activated (i.e., systole – the phase of the cardiac cycle when blood is being pumped out of the heart, which begins approximately 50 ms after the R-wave peak and lasts for about 250 ms, as indexed by the opening of the aortic valve that marks the end of the cardiac pre-ejection period and the left ventricular ejection time, respectively) are compared with responses to stimuli delivered while the baroreceptors are relatively quiescent (i.e., diastole – the phase of the cardiac cycle when blood is returning to the heart).

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Most of this type of cardiac cycle time research has investigated sensorimotor function. Early studies demonstrated that auditory (Saxon, 1970) and visual (Requin & Brouchon, 1964) stimuli were detected less accurately when presented during the QRS complex of the electrocardiogram, and, moreover, that simple reaction times to auditory (Birren, Cardon & Phillips, 1963) and visual (Callaway & Layne, 1964) stimuli were slowest when presented at the start of the cardiac cycle. These promising findings were interpreted in terms of interference caused by afferent baroreceptor inputs being integrated into medullary and cortical structures (for review see Carroll & Anastasiades, 1978). This evidence is also compatible with Lacey and Lacey's visceral afferent feedback hypothesis (1970, 1974, 1978, 1980), which contends that decelerations in heart rate facilitate external processing by unloading the baroreceptors to increase the flow of environmental information to the brain. Similarly, the intracardiac cycle paradigm (e.g., Birren et al., 1963), assumes that naturally-occurring variations in baroreceptor firing during the cardiac cycle can influence information processing, as reflected by changes in cortical, perceptual and sensorimotor responses. It is proposed that the diastolic phase of the cardiac cycle should be associated with improved information processing via decreases in blood pressure which unload the arterial baroreceptors to facilitate cortical activity whereas the systolic phase should be associated with debilitated information processing via increases in blood pressure which stimulate the arterial baroreceptors to inhibit cortical activity.

Doubts were raised over the robustness of the phenomenon when other researchers were unable to replicate the reported cardiac cycle time effects (Delfini & Campos, 1972; Elliott & Graf, 1972; Salzman & Jacques, 1976; Thompson & Botwinick, 1970; Weisz & Adam, 1996). It now seems likely that these null findings were due to the use of small sample sizes, insufficient sampling across the cardiac cycle and primitive equipment (cf. Carroll & Anastasiades, 1978) as recent large studies have repeatedly documented that simple reaction times are slowest for stimuli presented early in the cardiac cycle (Edwards, Ring, McIntyre, Carroll, & Martin, 2007; McIntyre, Ring, Hamer, & Carroll, 2007; McIntyre, Ring, Edwards, & Carroll, 2008). Other cardiac cycle time

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studies have generated neurophysiological evidence for pressor-related cortical interference. For instance, systole is associated with reduced auditory, visual and pain evoked potentials (Edwards, Inui, Ring, Wang, & Kakigi, 2008; Cohen, Lieb & Rist, 1980; Sandman, Walker, & Berka, 1982; Walker & Sandman, 1979; Walker & Sandman, 1982). Systole is also characterized by lower frequency electroencephalographic oscillations measured in the alpha band (Walker & Walker, 1983).

This evidence has been supplemented by neuroscientific research employing other baroreceptor stimulation protocols. A series of elegant studies have demonstrated that baroreceptor activation using neck suction methods is associated with a reduction in slow cortical negative potentials, such as the contingent negative variation, a measure of cortical arousal (for reviews see Elbert & Rau, 1995; Rau, Pauli, Brody, Elbert, & Birbaumer, 1993). This evidence proves that activation of the arterial baroreceptors can modulate cortical activity. These data raise the possibility that cognitive processes may also be susceptible to natural variations in arterial baroreceptor activity.

Up until recently, the available evidence has been extremely limited and confined to choice reaction time paradigms. One study presented an auditory or visual stimulus randomly during the cardiac cycle and required participants to indicate the sensory modality (Saari & Pappas, 1976). Responses were retrospectively classified as occurring during one of nine bins that were derived by dividing the R-R interval into nine equal periods. Choice reaction times were slower during the second bin compared to the fourth, sixth, and ninth bins. A second study (McIntyre et al, 2007) examined one, two and four choice reaction times to visual stimuli presented at one of six intervals (0, 150, 300, 450, 600, 750 ms) after the R-wave of the electrocardiogram. The intercept, a measure of the speed of sensorimotor processing, varied across the cardiac cycle whereas the slope, a measure of the speed of decision making, did not. Taken together, these two findings suggest that only sensorimotor processes, such as stimulus identification and response execution, but not

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cognitive processes, such as stimulus discrimination and response selection, are susceptible to baroreceptor-related interference.

However, this view needs to be revised in light of more recent cardiac cycle time studies of perception, visual selection and memory. A number of perception studies have demonstrated that stimulus intensity judgments are modulated by natural variations in barorceptor activation (Edwards, Ring, McIntyre, Winer, & Martin, 2009; Quelhas Martins, Ring, McIntyre, Edwards & Martin, 2009; Schulz, Reichert, Richter, Lass-Hennemann, Blumenthal & Schächinger, 2009; Wilkinson, McIntyre & Edwards, 2013). Using a visual masking paradigm to examine inhibitory processes in visual selection, Pramme, Larra, Schächinger and Frings (2014) showed that the ability of a mask to interfere with the detection of the subsequently-presented liminal target stimulus was reduced when the mask was presented 170 ms after the R-wave compared to 470 ms after the R-wave. Interestingly, the effect of the cardiac cycle affected the reduction of interference due to the mask rather than the direct processing of the target stimulus. Of most relevance for the present study, Garfinkel, Barrett, Minati, Dolan, Seth and Critchley (2013) presented a series of words on both the R-wave and T-wave of the ECG, and found that participants remembered fewer of the words that had been presented on the T-wave during a surprise free recall one hour later. They interpreted this finding as indicating that the effectiveness of encoding into memory was influenced by the timing of word stimuli and thereby cardiovascular arousal within the cardiac cycle. The findings of this latest study are compatible with the possibility that stimulation of the arterial baroreceptors can affect one or more of the processes involved in memory, such as stimulus encoding. This possibility warrants further investigation. Accordingly, the present study was designed to investigate variations in short-term memory processes as a function of the phase of the cardiac cycle.

Short-term memory was assessed here using a Sternberg task which requires encoding, storage and rehearsal of a set of sequentially presented digits, a brief maintenance period, the evaluation and serial comparison of a probe digit that might have been presented in the previous set

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followed by a binary response (Sternberg, 1966). Thus, the presentation of the probe is followed by a sequence of processing stages: stimulus encoding (to register the quality of the stimulus), serial comparison (that depends on the size of the positive set), a binary decision (to indicate whether the probe stimulus belonged among the set of remembered stimuli), and translation and organization of the response (Sternberg, 1969). Thus, on each trial of the Sternberg task, participants are required to identify the probe, compare the probe digit and the set of to-be-remembered digits, make a decision, and register a response. According to Sternberg (1969), the slope describing the linear increase in response latency per to-be-remembered digit represents the average duration of the comparison between the probe stimulus and each stimulus in the set of remembered stimuli. The intercept of the linear function is the response latency associated with a set of zero stimuli, and, therefore represents the combined durations of those processing components not associated with the comparison (i.e., probe identification, yes/no decision, and response selection). Accordingly, the slope and intercept represent relatively cognitive and sensorimotor measures of memory scanning performance (Madden & Blumenthal, 1989).

Based on the extant literature reviewed above, we hypothesized that naturally-occurring variations in baroreceptor stimulation would interfere with (and therefore slow) the information processing associated with probes presented during systole (i.e., when arterial baroreceptor activation is maximal) compared to probes presented earlier and later in the cardiac cycle. We also expected that the patterning of the key outcome variables (the slopes and zero intercepts) across the cardiac cycle would vary in form depending on the afferent lag associated with transmission and processing the stimulus, the afferent lag associated with baroreceptor stimulation, and the efferent lag associated with the motor response (see McIntyre, 2007).

Method

Participants

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One hundred (45 males, 55 females) healthy right-handed university students (*M* = 19.6, *SD* = 1.0 years of age), with a mean age of 20 (*SD* = 1) years, weight of 70 (*SD* = 13) kg, and height of 174 (*SD* = 9) cm, gave informed consent and volunteered to participate. They received course credit for participation. They had a mean resting heart rate of 76 (*SD* = 12) bpm, systolic blood pressure of 122 (*SD* = 10) mmHg, and diastolic blood pressure of 76 (*SD* = 9) mmHg. Heart rate was neither an inclusion nor exclusion criterion. Exclusion criteria comprised any known heart disease and any medication except birth control. Participants were asked to refrain from caffeine, alcohol, and exercise for 2 hours before testing. A local research ethics committee approved the study protocol.

Physiological Measurements

Resting blood pressure and heart rate were measured with a validated (O'Brien et al., 2001) oscillometric sphygmomanometer (HEM-705CP, Omron) attached to the participant's left arm. An electrocardiogram was recorded continuously with three spot electrodes (Cleartrace, ConMed) in a modified chest configuration; the active electrodes were placed on the right clavicle and lower left rib and a reference electrode was placed on the left clavicle. The electrocardiographic signal was amplified and filtered (0.1–100 Hz plus 50 Hz notch filter) by an AC amplifier (P511, Grass) and then digitised at 2500 Hz with 16-bit resolution and recorded using Spike2 and a Power1401 (Cambridge Electronic Design).

Sternberg Task.

A version of the Sternberg short-term memory task (Sternberg, 1966) was used to assess performance. Participants sat quietly facing a stimulus box that was located 1 m in front of them and kept a response box under their dominant hand. The stimulus box contained a single 40 mm wide by 55 mm high dual-color (green, red) 7-segment light emitting diode panel that was used for presenting warning, experimental, probe and feedback stimuli. The response box contained two

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low force microswitch levers (D459-V3LD, Cherry). A Spike2 (Cambridge Electronic Design) computer program ran the experiment and collected button press responses via a Power1401 (Cambridge Electronic Design).

Two blocks of 48 trials separated by a 3-min rest period were completed. Participants were required to depress the two levers on the response box with the index and middle fingers of their dominant hand to initiate each trial. The computer program waited until both response levers were depressed before starting a trial. A sequence of either two or six green single-digit numbers, ranging from 0 to 9 and without repetition, was serially presented. Each number was visible for 750 ms with a 250 ms interval between numbers. Participants were required to memorize this set of numbers. After a 3000 ms delay, a red probe number was presented for 750 ms. Participants were required to decide whether the probe was included in the previous set of green numbers by lifting the index finger for matching probes and the middle finger for mismatching probes. Performance feedback concluded the trial: correct decisions were followed by a green U for 750 ms whereas a red U was presented for 750 ms after incorrect responses. Participants were instructed to respond as rapidly as possible while keeping errors to a minimum. The set of green numbers changed from trial to trial. The numbers were presented in a non-repeating counterbalanced fashion. Moreover, trial type was pseudo-random within each block, with the constraint that there could be no more than three consecutive trials of each set size (2 or 6) and probe type (match or mismatch).

Procedure

Participants completed a single session. Following instrumentation, rest and blood pressure measurement, participants were instructed about the task demands. They then performed 24 practice trials before completing 96 experimental trials of the Sternberg task

Data Reduction and Analysis

Response latency (ms) was calculated as the time between the onset of the probe stimulus and the release of the switch lever. A trial was discarded if the latency was less than 100 ms (i.e.,

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anticipation error) or greater than 2250 ms (i.e., inattention error), or if the participant lifted both fingers concurrently (< 100 ms apart): The percentage error (M = 7.12, SD = 5.60) was very low. Accordingly, only correct responses were included in the analysis reported below. The R-wave latency relative to probe onset (ms) was measured in each trial. In line with previous research (e.g., Birren et al., 1963; Edwards et al., 2008; Saari & Pappas, 1976), trials were then sorted retrospectively into one of six 100 ms wide intervals (with each interval labelled by its midpoint), whose minimum and maximum indicated the timing of probe onset after the R-wave: 0–99 ms (R+50 ms), 100–199 ms (R+150 ms), 200–299 ms (R+250 ms), 300–399 ms (R+350 ms), 400–499 ms (R+450 ms), and 500–599 ms (R+550 ms). The mean numbers of trials per interval were 6.09, 5.98, 6.12, 6.36, 6.21 and 5.54 respectively for set size 2 and 5.88, 5.96, 5.98, 5.81, 5.76 and 5.60 respectively for set size 6. Thus, the overall number (%) of utilized trials was 71.31 (76%). The mean response latencies per interval per set size are shown in Table 1 (see Appendix). The slope (ms per digit), a measure of the time required to process one additional digit in memory, and the zero intercept (ms), a measure of sensorimotor processing time, were computed for each interval (Sternberg, 1966).

Analyses of Variance (ANOVAs), with R-wave to probe interval (R+50, R+150, R+250, R+350, R+450, R+550 ms) as a within subjects factor, were conducted using the multivariate method (Vasey & Thayer, 1987). We report partial eta-squared ($\eta^{2)}$ as an effect size. We used the Wilks' lambda multivariate test. Since we were interested in the patterning of the variables across the cardiac cycle any statistically significant main effect for interval was followed by polynomial trend analysis. All analyses were conducted using SPSS 20 software.

Results

A 6 R-wave to probe interval (R+50, R+150, R+250, R+350, R+450, R+550 ms) ANOVA conducted on the slopes confirmed a main effect for interval, $F(5, 95) = 2.33$, $p < .05$, $\eta^2 = .11$. Information processing per additional digit was faster for probes presented during the early

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compared to those presented in the later phase of the cardiac cycle (see Figure 1a). The slopes were characterized by a cubic trend, $F(1, 99) = 5.83$, $p < .05$, $\eta^2 = .06$, with two inflection points (i.e., changes in direction), across the cardiac cycle. The observed change of curvature from concave to convex fits a model in which the baroreceptor afferent traffic changes from inactive to active to inactive one cardiac cycle, followed by a subsequent adjoining cycle of the same form.

A repeated measures ANOVA (6 intervals) conducted on the zero intercepts revealed a main effect for interval, $F(5, 95) = 2.86$, $p < .05$, $\eta^2 = .13$. Basic sensorimotor processing and responding were greater during the early phase of the cardiac cycle compared to later (see Figure 1b). The zero intercept was characterized by a cubic trend, $F(1, 99) = 8.16$, $p < .005$, $\eta^2 = .08$, with an early convex and later concave patterning across the cardiac cycle,

Discussion

Our study investigated cardiac cycle time effects for a short-term memory task. In the context of the Sternberg task, memory (retrieval and comparison) processing was slowed for comparison stimuli presented 300 ms to 600 ms after the R-wave compared to those presented earlier in the cardiac cycle. In contrast to the null findings of previous choice reaction time studies (McIntyre et al, 2007; Saari & Pappas, 1976), we showed that natural variations in arterial baroreceptor activity can influence cognitive processes. Specifically, our slope results are in broad agreement with cardiac cycle time studies showing that natural variations in baroceptor activation can impact judgments of stimulus intensity (Edwards, et al, 2009; Quelhas Martins, et al., 2009; Schulz et al., 2009; Wilkinson, et al., 2013), masking of primes (Pramme, et al., 2014) and memory encoding for words (Garfinkel, et al., 2013). The cycle time effect for the slope measure can be attributed to the effects of baroreceptor stimulation on retrieval and/or comparison processes since the effect was based on the presentation of the probe stimulus at different times after the onset of the heartbeat. Accordingly, this effect is different to that reported by Garfinkel and colleagues who

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noted differences in the ability to recall stimuli presented (and therefore encoded) at different times after the onset of the heartbeat.

Although the mechanism responsible for our cycle time effect has yet to be established, the observed modulation favours the suggested cortical impact of arterial baroreceptor afference (Birren et al, 1963) that has become known as the visceral afferent feedback hypotheses (Lacey & Lacey, 1974), whereby the transmission of information about the state of the cardiovascular system may have interfered with short-term memory retrieval and/or comparison processes. In our study, the form of the cardiac cycle effect was cubic. This patterning fits a model in which baroreceptors are quiet, active and quiet in one cardiac cycle, followed by a subsequent cycle of the same form. The form of the cardiac cycle time effect depends on a number of factors, including afferent transmission delays of the stimulus and the baroreceptors, the processing lags of both these afferent signals due to the different brain areas involved, as well as efferent transmission delays of the response (McIntyre, 2007). This can help explain why the form of the cycle time effect was different for the slope and intercept measures, with the former requiring more cortical processing than the latter, and, therefore, the effect of baroreceptor activation was manifested later in the cycle.

In line with research showing that simple reaction times are slower for imperative stimuli presented early in the cardiac cycle (Birren et al., 1963; Callaway et al., 1964; Edwards et al., 2007; McIntyre et al., 2007; 2008), we found that the zero intercept, a measure of basic sensorimotor processing, was greater for probe stimuli presented temporally proximal to the R-wave. Our findings thereby illustrate that the pattern of the cycle time effect differs for basic sensorimotor processes and memory retrieval and comparison processes. These data add to our appreciation of the nature of the cardiac-cortical relationship, whereby the patterning of the cycle time effect varies in form and latency with the complexity and/or duration of the response in question (Edwards et al., 2001; 2009). Specifically, the cycle time effect appears to depend on the duration of the stimulus presented, peripheral and central nerve conduction and processing latencies, and the extent to which

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the task-related information processing is amenable to baroreceptor-related changes in cortical arousal and activation (Lacey & Lacey, 1970, 1974, 1978, 1980).

The findings of the current study, which were based on a large sample using a well validated methodology and sophisticated recording equipment, revealed medium-sized (Cohen, 1992) cardiac cycle time effects for both memory and sensorimotor processes. Nevertheless, they need to be interpreted in light of some potential shortcomings. First, to standardize the retention period of the task at three seconds for every trial we opted to score the data by retrospectively determining the timing of probe onset relative to the R-wave. This feature that ensured task difficulty was standardized but consequently allowed no control over the timing of stimulation within the cardiac cycle. Second, performance was only analysed up to 600 ms after the R-wave. Although some participants had slower heart rates that would have permitted examination of performance later in the cycle this was not possible for many others, and, accordingly, we restricted the window to R+0 ms to R+600 ms. Third, measuring response latency to probe stimulus onset did not allow us to separate baroreceptor stimulation effects on memory encoding (during the presentation of the digit set) and retrieval and comparison processes (during probe presentation). Fourth, we only employed two set sizes in our implementation of the Sternberg task. Our rationale for doing so was that the slope is linear and therefore sets of two and six stimuli should adequately capture the change in response latency with increasing memory load. According to Sternberg (1966) *"The linearity of the latency functions suggests that the time between test stimulus and response is occupied, in part, by a serial-comparison (scanning) process"* (p. 653). The slope measure provides information on the time required to process each addition increase in set size and can therefore be computed with only two sets since the function is linear. It may also be worth noting that our intercept values were somewhat greater than those reported by Sternberg (1966) and more in line with those reported by Madden and Blumenthal (1989). Finally, the findings were collected using only one task, and, therefore studies are required that test the generalizabilty of the effect to other high order cognitive functions using other paradigms. Evidence that sensory evoked potentials (e.g., Sandman et al.,

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1982; Walker et al., 1979; Walker et al., 1982) and cortical oscillations (Walker & Walker, 1983) vary as a function of the phase of the cardiac cycle, provide encouragement for researchers wishing to explore cardiac cycle time effects using the classic paradigms developed by cognitive neuroscientists.

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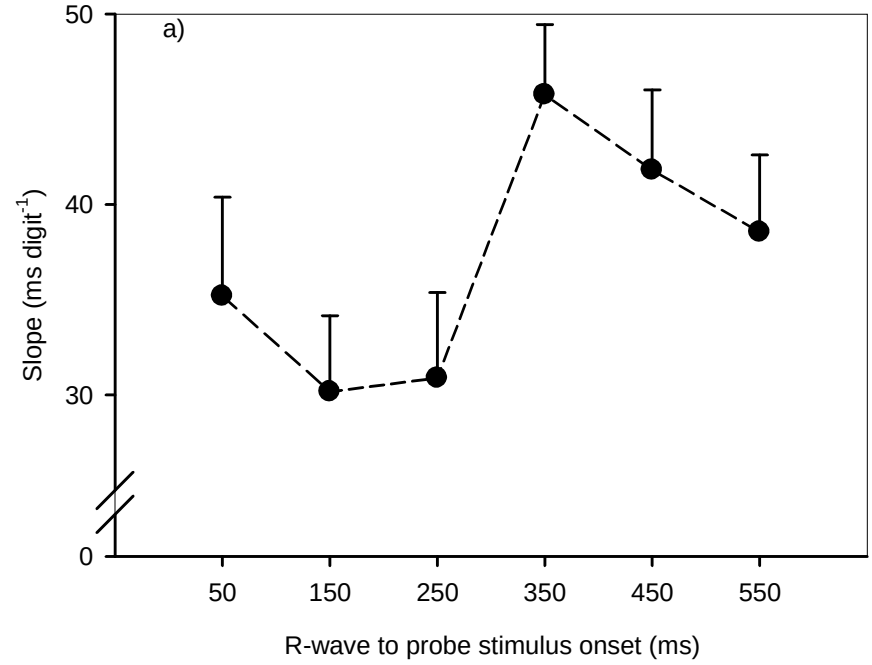
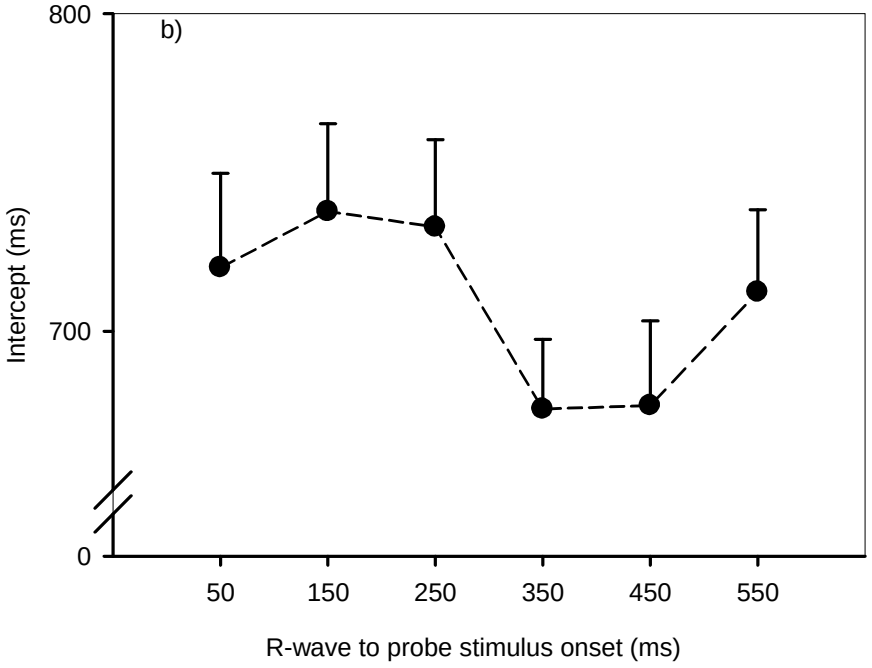
Figure 1. Mean (*SE*) slopes (top panel, a) and zero intercept latencies (bottom panel, b) for comparison probe stimuli delivered across the cardiac cycle.





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Appendix

Table 1. Mean response latencies per interval per set size.

R-wave to Probe Stimulus Onset (ms)	Memory Set Size	
	2	6
50	790	931
150	798	919
250	795	918
350	767	950
450	760	927
550	789	944

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